Remarks/Arguments

Supplemental IDS Submitted on January 11, 2008

The Examiner has returned a copy of the PTO/SB/08 form submitted by Applicants on January 11, 2008 with his signature and date of consideration. Applicants respectfully request that the Examiner also initial each reference to indicate that he has considered it.

Supplemental IDS Submitted on April 25, 2008

Applicants submitted on April 25, 2008 a Supplemental IDS and a fee under CFR §1.17(p). It is respectfully requested that the publications cited in the Supplemental IDS be considered by the Examiner and made of record in this application.

Claim Rejections Under 35 USC § 112, First Paragraph

The Examiner suggests that claims 1-4, 6-7, 10, 13-16 and 21-24 fail to comply with the enablement requirement under 35 USC § 112, first paragraph. More particularly, the Examiner alleges that the specification does not support the use of the presently claimed combinations in the treatment of lung cancer. We respectfully request reconsideration of this rejection.

The Examiner is asked to consider the Rosano et al. publication discussed in applicant's response to the last office action (Rosano et al. Cancer research 2007; 67(13); 6351 to 6359, on the record). Rosano et al. show that the combination of ZD4054 and ZD1839 provides an enhanced anti-tumour effect in HEY and OVCA 433 ovarian cancer lines. Rosano et al also show that stimulation of cells with endothelin-1 promotes transactivation of EGFR thus establishing that there is cross-signaling between EGFR and endothelin-A receptor pathways. Rosano et al state that this provides a rationale for combining an EGFR tyrosine kinase inhibitor with an Endothelin-A receptor antagonist (see Rosano et al abstract, last 4 lines).

The Examiner correctly points out that Rosano et al only disclose ovarian cancer cell lines. However, it is respectfully submitted that the disclosure in Rosano et al demonstrating the existence of cross talk between EGFR and the endothelin-A receptors, suggests that this fundamental signaling mechanism would also be expected to be present in other tumours that express both of these receptors.

It was well known at the filing date of the present application that many cancers express endothelin-A receptors, for example, the Examiner is asked to consider the review article by Nelson et al. (Exhibit A: Nature Reviews Cancer, 2003;3; 110-116, on the record). Nelson et al state that the endothelin-A receptor is expressed in a wide range of tumours including prostate, ovarian, lung, colon, renal, cervical, melanoma and glioma (see Nelson et al p112, col 1 and table 2, page 114).

It was also well known at the filing date of the present application that EGFR is over-expressed in many tumour types as set out in the present application at para [0012]. In particular EGFR over expression is observed in lung cancer and recently EGFR tyrosine kinase inhibitors such as Iressa and Tarceva have been approved for use in the treatment of advanced lung cancer.

Over-expression of these two receptors was also well known in other tumours such as prostate cancer at the filing date of the present application. In support of this the Examiner is asked to consider Godara et al (Exhibit B: Urology 70: 209–215, 2007, on the record) showing that Endothelin-A is over-expressed and Lorenzo et al. (Exhibit C: Clinical Cancer Research, *Vol. 8, 3438–3444, November 2002,* 3438, on the record).

Based upon the finding in Rosano et al of cross-signaling between the EGFR and endothelin-A receptor signaling pathways, it is reasonable to expect that such cross-signaling would be present in tumours that express both EGFR and endothelin-A receptors. As discussed above, it is clear that these two receptors are expressed in a number of tumours, including lung, prostate and ovarian cancers. Rosano et al also show that a combination according to the present invention provides an enhanced anti-tumour effect in cell lines that express both EGFR and endothelin-A receptors.

It is respectfully submitted that the present application clearly provides enablement of the invention at for example para. [0018]. This expressly states that the presently claimed combinations are suitable for use in the treatment of cancers that express both endothelin-A and EGFR. The findings of Rosano et al of cross signaling between EGFR and endothelin-A provide additional support to the teaching and enablement that is already present in the current application. Furthermore, the present application provides examples and guidance on suitable doses and means for administering both ZD4054 and the EGFR TKI. In view of the support provided by in Rosano et al and the information provided in the application it is submitted that a skilled person would be able to use the presently claimed invention without undue experimentation.

The Examiner is therefore respectfully requested to reconsider and withdraw this objection.

Although Applicants believe no additional fees are due, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. 100864-1P US.

Respectfully submitted,

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